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Biological agent experience in patients with Familial Mediterranean Fever: Real-life data

Biological agents and familial mediterranean fever

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Abstract
Aim: The aim of this study is to evaluate the frequency and type of biological agent use in patients with familial Mediterranean fever (FMF) in our tertiary medical center.
Materials and Methods: A total of 734 adult patients (246 males and 488 females) diagnosed with FMF who were admitted to our Rheumatology Outpatient Clinic between January 2014- January 2019 were included in this study. Age, sex, family history, frequency of attack, presence of amyloidosis, use of biological therapy, history of concomitant disease, colchicine doses, use of additional treatments, presence of sacroiliitis, prolonged arthritis, and MEFV gene analysis were recorded based on the history obtained at the admission toour rheumatology outpatient clinic.
Results: A total of 81 FMF patients (11 %) were found to be treated with biological agents. Anti-TNF agents were the most frequently used biological treatment [6.3 % (n = 46)]. Anakinra usage was 3.8% (n = 28). MEFV gene mutations were positive in 77.7% (n = 570) patients and M694V gene mutation was the most commonly observed gene mutation [17.9% (n = 131)].
Discussion: In the present study, anti-TNF agents were the most frequently used biological treatment.They were mostly preferred due to sacroiliitis and chronic arthritis clinic in our FMF group, than IL-1 blockers.
Keywords
FMF; MEFV Gene Mutation; Colchicine Resistance; Biological Agent

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent fever attacks and serosal inflammation. FMF is more often seen in the Mediterranean region; it is common in Sephardic Jewish, Armenian, Arab and Turkish populations [1,2]. Recent studies have reported that more than 100,000 FMF patients are found worldwide, and the ratio for the Turkish population is stated as 1/1073 [3]. Although the etiopathogenesis of the disease is not clearly understood; the proinflammatory process initiated by MEFV (Mediterranean Fever) gene mutation is thought to reveal the disease [4]. The most common 3 mutations are M694V, E148Q, V726A, and a MEFV gene mutation has been found in more than 70% of FMF cases [5]. The most common gene mutation in the study of the Turkish FMF working Group of 1090 Turkish patients was stated to be M694V [6].

In 90% of patients with familial Mediterranean fever, clinical findings have an onset before the age of twenty. The classical clinical picture of the disease constitutes fever, abdominal pain, chest pain due to the attacks of polyserositis, joint findings and skin findings [7]. Vasculitic diseases such as Henoch Schönlein purpura (HSP), Polyarteritis nodosa (PAN) can also be seen during the course of the disease [8]. Amyloidosis is the most important complication worsening the prognosis of FMF. Amyloidosis especially affects the kidneys and may cause chronic renal failure [9]. The regular use of colchicine reduces the frequency and severity of attacks and has been shown to prevent the development of amyloidosis [10].

In FMF, biological drugs are used for three purposes: Firstly, to provide control of attacks due to colchicine resistance or intolerance; Secondly, for the treatment of amyloidosis and to prevent the development of renal failure; Thirdly, for the treatment of chronic arthritis or concomitant sacroiliitis. It is recommended to use with colchicine in all three [11]. The most commonly used IL-1 blocking biological agents are anakinra and canakinumab [12,13]. In FMF related sacroiliitis and resistant arthritis, anti-TNF agents as infliximab, adalimumab, golimumab, certolizumab and etanercept are preferred [14,15].

In this study, we aimed to investigate the frequency and type of biologic agent use in patients of FMF in our tertiary medical center.

Material and Methods

A total of 734 adult patients (246 males and 488 females) , diagnosed with FMF according to Livneh diagnostic criteria [16] who were admitted to our Rheumatology Outpatient Clinic between January 2014- January 2019 were included in this study. The data of patients diagnosed as FMF were recorded retrospectively by scanning patient files. Age, sex, family history, frequency of attacks, presence of amyloidosis, use of biological therapy, comorbid disease history, colchicine treatment doses, use of additional treatments, presence of sacroiliitis, presence of arthritis, and MEFV gene analyses results were recorded. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

In this study, SPSS (version 22) for Windows was used for statistical analysis. Descriptive statistics and continuous variables are shown as the mean ± standard deviation or median (minimum and maximum); categorical variables are shown as the number of cases and percentages (%). In the comparisons, the Kolmogorov-Smirnow test was used to determine the distribution of all continuous variables, and non-parametric statistical methods were used for the variables showing a skewed distribution. In comparisons between groups, the Kruskall-Wallis H test was used for multiple groups, the Mann-Whitney U test was used for paired groups and cross-table statistics were used to compare categorical variables (the Chi-square and the Fisher's Exact Test). Statistical significance was set at $p < 0.05$.

Results

The mean age of 734 patients who were followed-up in our center was 38.84 ± 13.79 years (14-81). Of the 734 patients included, 33.5% were male (n = 246) and 66.5% were female (n = 488); 61.3% of the patients had a family history of FMF (n = 450). Clinical and demographic findings of patients are shown in Table 1.

Table 1. Clinical and demographic findings of FMF patients

Medium Age	38,84 ± 13,79 years/old
Gender Male Female	 33.5 % (n=246) 66.5 % (n=488)
FMF Family History	61.3 % (n=450)
Arthritis/arthralgia	49.5 % (n=450)
Sacroiliitis	12.3 % (n=90)
Amyloidosis	10.2 % (n=75)
Chronic renal failure	10.9 % (n = 80)
Hypertension	2.3 % (n = 17)
Type 2 Diabetes Mellitus	1.9 % (n = 14)
Lung Disease	0.5 % (n = 4)

In our study, 75.6% of the FMF patients were in complete remission without any attack, 7.9 % had 1-2 attacks per year; 3.1 %, 1-2 attacks per six month; 3.4 %, 1-2 attacks per three month; 2.2 %, 1-2 attacks per two month and 7.8 %, 1-2 attacks per month consecutively.

At least one MEFV gene mutation was positive in 77.7% (n = 570) of the patients in our study group. When the frequency of gene mutations was compared, M694V gene mutation was the most common gene mutation. The patient group with M694V gene mutation was found to be 23.3% (n = 171). Other MEFV gene mutations and subgroup sequencing were determined as indicated in Table 2.

When the patients were classified in terms of colchicine doses, 3.7% (n = 27) of patients received 0.5 mg / day treatment dose, 45.2% (n = 332) 1 mg / day, 39.5% (n = 290) 1.5 mg / day treatment dose) and 2 mg / day treatment dose was in 11.6% (n = 85).

The other drugs used by the patients were sulfasalazine 8.6% (n = 63), methotrexate 3.8% (n = 28), hydroxychloroquine 2.7% (n = 20), corticosteroids 2.5% (n = 18), and azathioprine 1.1% (n = 8).

Table 2. Distribution of MEFV gene mutations in patients

Mutation Type	Patient number	Percent (%)
Negative	164	22.3
Non-M694V Compound Heterozygote	112	15.3
M694V Heterozygote	97	13.2
E148Q Heterozygote	87	11.9
M694V Homozygote	74	10.1
V726A Heterozygote	59	8.0
M680I Heterozygote	53	7.2
P369S Heterozygote	25	3.4
M680I Homozygote	14	1.9
E148Q Homozygote	14	1.9
F479L Heterozygote	6	0.8
K695R Heterozygote	4	0.5
A744S Heterozygote	4	0.5
R761 Heterozygote	3	0.4
R202Q Homozygote	3	0.4
R202Q Heterozygote	2	0.3
Total	**734**	**100**

A total of 81 patients (11 %) treated with biological agents were identified. Anti-TNF was the most frequently used biological therapy [6.3 % (n = 46)]. Anakinra was used in 3.8% (n = 28). The frequency of other biologic drugs use was as follows: etanercept 3% (n = 22), adalimumab 1.5% (n = 11), infliximab 1% (n = 7), golimumab 0.7% (n = 5), canakinumab 0.5% (n = 4), sekukinumab 0.4% (n = 3) and certolizumab 0.1% (n = 1). (Table 3).

Although not statistically significant, 21 of 28 patients using Anakinra, 518 of 653 patients using colchicine and 31 of 53 patients using anti-TNF alpha treatment were positive for a MEFV mutation. M694V was the most common gene mutation in 28 patients using anakinra (n = 6). Five of these patients were M694V homozygous and one of them was M694V heterozygous.

Table 3. Comparison of biological treatments used in FMF patients

Anakinra	3.8 % (n=28)
Etanercept	3 % (n=22)
Adalimumab	1.5 % (n=11)
Infliximab	1 % (n=7)
Golimumab	0.7 % (n=5)
Canakinumab	0.5 % (n=4)
Secukinumab	0.4 % (n=3)
Certolizumab	0.1 % (n=1)
No biologic treatment	89 % (n=653)

Discussion

In the present study, a total of 81 FMF patients (11 %) were on biologic drugs; 6.3 % used anti-TNF alpha therapy and 4.3% used IL-1 therapy. The most frequently used biologic agent group was anti-TNF, and as expected M694V was the most frequent gene mutation.

At our clinic, IL-1 blockers (Anakinra, canakinumab) were the first choice for colchicine-resistant FMF or amyloidosis; anti TNF agents have been used as the first choice in the presence of sacroiliitis and chronic arthritis. Of the 81 patients receiving biological treatment, 40 % received IL-1 blocker and 60 % received anti-TNF treatment.

Amyloidosis is the most serious complication of FMF caused by amyloid A (AA type) protein deposition and presents as progressive nephropathy causing end-stage renal failure [17]. In a study on 2246 FMF patients, in Turkey, amyloidosis rate was 8.6% . In the same study, M694V mutation was found to increase risk of the development of amyloidosis [18]. The rate of amyloidosis in our study was 10.2% (n = 75) in 734 patients. While development of amyloidosis is related to FMF, the presence of spondyloarthritis and chronic arthritis additionally may increase the risk, at least in some of patients.

In our study, 63 cases (9.9%) had 4 or more FMF attack episodes in 6 months and this rate was similar to the findings in other studies [19]. In a systematic review of a 100 cases, IL-1 blockers were evaluated in patients with colchicine-resistant FMF; 76.5% of cases with anakinra, 67.5% cases with canakinumab have been shown to provide complete remission [20]. In a retrospective study of 172 cases, the rates were found to be 40 and 65%, respectively [19]. In addition, IL-1 blockers have been shown to be effective in FMF-induced amyloidosis cases; secondary to suppression of inflammation, causing regression of proteinuria, and even they have positive effect in cases of end-stage renal failure due to amyloidosis [20].

In our study, arthralgia/arthritis was found in 49.5% (n = 450) and sacroiliitis in 12.3% (n = 90) of the patients. In a study by Samuels et al., arthritis was found to be the third most common clinical presentation after fever and abdominal pain with a frequency of 45% [21]. In the study conducted by the Turkish FMF group, arthritis was found with a frequency of 47.4% [22]. In another study from Turkey, sacroiliitis rate was 7% in 256 FMF patients. In the same study, the frequency of M694V mutation was reported to be 93.7% in patients with FMF who had sacroiliitis [23]. Anti-TNF treatment is used for the indication of sacroiliitis/chronic arthritis in FMF cases, has been reported to have positive effects also on FMF attacks [24]. In another case of FMF with amyloidosis and sacroiliitis registered in our center, it was reported that proteinuria decreased by anti -TNF treatment [25].

It is known that the presence of M694V mutation is a poor prognostic factor in FMF and is associated with the development of amyloidosis. In our study, MEFV gene mutation positivity was in 77.7% (n = 570) in FMF patients. When the frequency of gene mutations was compared, M694V gene mutation was the most common gene mutation in FMF patients. Furthermore, M694V was the most common gene mutation in 28 patients using anakinra (n = 6). Five of these patients were M694V homozygous and one of them was M694V heterozygous.

In the present sudy, it was shown that biologic treatment is necessary in some of the FMF patients. Anti TNF agents were mostly being preferred due to sacroiliitis and chronic arthritis clinic in our FMF group than IL-1 blockers.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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